To: jcruse@umc.edu, jskreutz@vcu.edu, nzasler@cccv-ltd.com, plosone@plos.org

Subject: Duplicate Publication

Duplicate Publication Articles:

1) Min Hu and Bo Liu. Resveratrol attenuates lipopolysaccharide-induced dysfunction of blood-brain barrier in endothelial cells via AMPK activation. **Korean J Physiol Pharmacol**, 2016 Jul; 20(4): 325-332. (https://doi.org/10.4196/kjpp.2016.20.4.325)

2) Hai-Ya Yu, Yu-Bing Cai & Zhan Liu. Activation of AMPK improves lipopolysaccharideinduced dysfunction of the blood–brain barrier in mice. **Brain Injury**, 2015; 29(6): 777–784. (http://dx.doi.org/10.3109/02699052.2015.1004746)

3) Zhihong Zhao, Jue Hu, Xiaoping Gao, Hui Liang, Zhan Liu. Activation of AMPK attenuates lipopolysaccharide-impaired integrity and function of blood–brain barrier in human brain microvascular endothelial cells**. Experimental and Molecular Pathology**, 97 (2014) 386–392. (http://dx.doi.org/10.1016/j.yexmp.2014.09.006)

4) Long Zhao, Li-Na Sun, Hui-Bin Nie, Xue-Ling Wang, Guang-Ju Guan. Berberine Improves Kidney Function in Diabetic Mice via AMPK Activation. **PLOS ONE**, 2014; 9(11):e113398 (DOI: 10.1371/journal.pone.0113398)

Date: January 10, 2017

Dear J.M. Cruse (Exp Mol Pathol), J.S. Kreutzer and N.D. Zasler (Brain Inj), Joerg Heber (PLOS ONE)

We are the Editors-in-Chief of Korean Journal of Physiology & Pharmacology (KJPP). We have been advised that apparently a paper published in our journal had been previously published in almost identical form in your Journals (Brain Inj, 2015; 29(6): 777–784; Exp Mol Pathol, 97 (2014) 386–392).

The version as published in our Journal (KJPP) was:

1) Min Hu and Bo Liu. Resveratrol attenuates lipopolysaccharide-induced dysfunction of blood-brain barrier in endothelial cells via AMPK activation. Korean J Physiol Pharmacol 2016 Jul; 20(4): 325-332. (https://doi.org/10.4196/kjpp.2016.20.4.325)

Korean J Physiol Pharmacol 2016;20(4):325-332
http://dx.doi.org/10.4196/kjpp.2016.20.4.325

KJPP

Original Article

Resveratrol attenuates lipopolysaccharide-induced dysfunction of blood-brain barrier in endothelial cells via AMPK activation

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Key Words
AMPK
Blood -brain barrier
LPS
NAD(P)H oxidase
Resveratrol

ABSTRACT Resveratrol, a phytoalexin, is reported to activate AMP-activated protein kinase (AMPK) in vascular cells. The blood-brain barrier (BBB), formed by specialized brain endothelial cells that are interconnected by tight junctions, strictly regulates paracellular permeability to maintain an optimal extracellular environment for brain homeostasis. The aim of this study was to elucidate the effects of resveratrol and the role of AMPK in BBB dysfunction induced by lipopolysaccharide (LPS). Exposure of human brain microvascular endothelial cells (HBMECs) to LPS (1 μg/ml) for 4 to 24 hours week dramatically increased the permeability of the BBB in parallel with lowered expression levels of occluding and claudin-5, which are essential to maintain tight junctions in HBMECs. In addition, LPS significantly increased the reactive oxygen species (ROS) productions. All effects induced by LPS in HBVMCs were reversed by adenoviral overexpression of superoxide dismutase, inhibition of NAD(P)H oxidase by apocynin or gain-function of AMPK by adenoviral overexpression of constitutively active mutant (AMPK-CA) or by resveratrol. Finally, upregulation of AMPK by either AMPK-CA or resveratrol abolished the levels of LPS-enhanced NAD(P)H oxidase subunits protein expressions. We conclude that AMPK activation by resveratrol improves the integrity of the BBB disrupted by LPS through suppressing the induction of NAD(P)H oxidase-derived ROS in HBMECs.

The versions as published in your Journals (Brain Injury, Exp Mol Pathol, PLOS ONE) were:

1) Hai-Ya Yu, Yu-Bing Cai & Zhan Liu. Activation of AMPK improves lipopolysaccharideinduced dysfunction of the blood–brain barrier in mice. Brain Inj, 2015; 29(6): 777–784. (http://dx.doi.org/10.3109/02699052.2015.1004746)

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 DOI: 10.3109/02699052.2015.1004746

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ORIGINAL ARTICLE

Activation of AMPK improves lipopolysaccharide-induced dysfunction of the blood–brain barrier in mice

Hai-Ya Yu[1], Yu-Bing Cai[2], & Zhan Liu[1,3]

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Abstract

Primary objective: Lipopolysaccharide (LPS) is known to alter the integrity of the blood–brain barrier (BBB) in sepsis, although the underlying mechanism remains unknown. The aim of this study was to elucidate the molecular mechanisms underlying disruption of the BBB in LPS-induced sepsis.
Research design: Both *in vitro* and *in vivo* experiments were designed to test the role of AMP-activated protein kinase (AMPK) in LPS-induced BBB dysfunction.
Methods and procedures: Human brain microvascular endothelial cells (HBMECs) were cultured. The protein expressions were detected by western blot. BBB integrity was determined by Evans Blue.
Main outcomes and results: LPS (1 $\mu g ml^{-1}$) dramatically increased the permeability of the BBB and the ROS productions, as well as reducing the expression levels of occludin and claudin-5 in cultured HBMECs. Inhibition of NAD(P)H oxidase by apocynin or up-regulation of AMPK reversed the LPS-induced abnormities in HBMECs. In LPS-induced sepsis in mice, it was found that LPS dramatically increased NAD(P)H oxidase protein expressions and ROS productions in the brain and disrupted BBB function assayed by Evans blue staining, which were abolished by AICAR treatment.
Conclusions: It is concluded that AMPK activation improves the functions of the BBB impaired by LPS through suppression of NAD(P)H oxidase-derived ROS in mice.

Keywords
Ageing, AMPK, BBB, LPS, NAD(P)H oxidase, ROS

History
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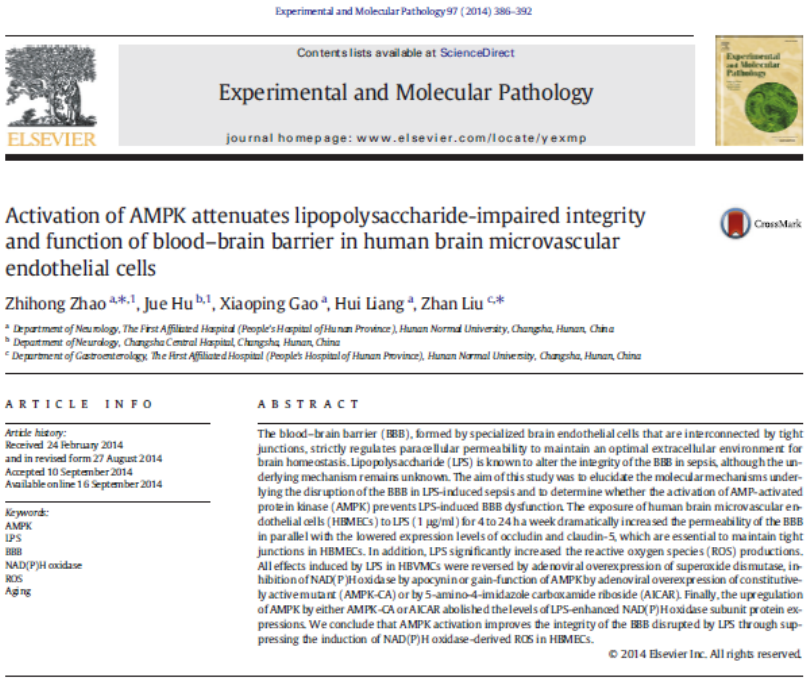
2) Zhihong Zhao, Jue Hu, Xiaoping Gao, Hui Liang, Zhan Liu. Activation of AMPK attenuates lipopolysaccharide-impaired integrity and function of blood–brain barrier in human brain microvascular endothelial cells. Experimental and Molecular Pathology 97 (2014) 386–392. (http://dx.doi.org/10.1016/j.yexmp.2014.09.006)



Experimental and Molecular Pathology 97 (2014) 386–392

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Activation of AMPK attenuates lipopolysaccharide-impaired integrity and function of blood–brain barrier in human brain microvascular endothelial cells

Zhihong Zhao [a,*,1], Jue Hu [b,1], Xiaoping Gao [a], Hui Liang [a], Zhan Liu [c,*]

[a] Department of Neurology, The First Affiliated Hospital (People's Hospital of Hunan Province), Hunan Normal University, Changsha, Hunan, China
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Keywords:
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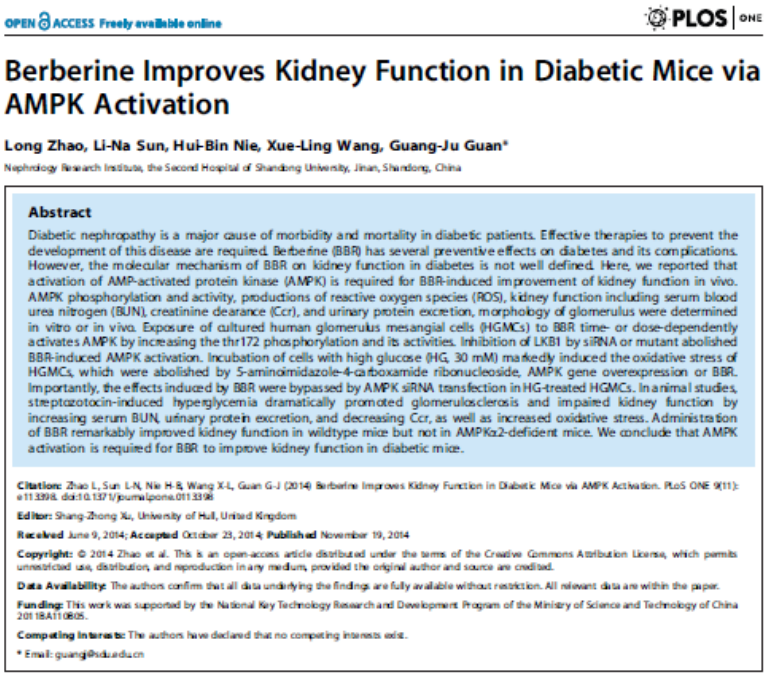
ABSTRACT

The blood–brain barrier (BBB), formed by specialized brain endothelial cells that are interconnected by tight junctions, strictly regulates paracellular permeability to maintain an optimal extracellular environment for brain homeostasis. Lipopolysaccharide (LPS) is known to alter the integrity of the BBB in sepsis, although the underlying mechanism remains unknown. The aim of this study was to elucidate the molecular mechanisms underlying the disruption of the BBB in LPS-induced sepsis and to determine whether the activation of AMP-activated protein kinase (AMPK) prevents LPS-induced BBB dysfunction. The exposure of human brain microvascular endothelial cells (HBMECs) to LPS (1 μg/ml) for 4 to 24 h a week dramatically increased the permeability of the BBB in parallel with the lowered expression levels of occludin and claudin-5, which are essential to maintain tight junctions in HBMECs. In addition, LPS significantly increased the reactive oxygen species (ROS) productions. All effects induced by LPS in HBVMCs were reversed by adenoviral overexpression of superoxide dismutase, inhibition of NAD(P)H oxidase by apocynin or gain-function of AMPK by adenoviral overexpression of constitutively active mutant (AMPK-CA) or by 5-amino-4-imidazole carboxamide riboside (AICAR). Finally, the upregulation of AMPK by either AMPK-CA or AICAR abolished the levels of LPS-enhanced NAD(P)H oxidase subunit protein expressions. We conclude that AMPK activation improves the integrity of the BBB disrupted by LPS through suppressing the induction of NAD(P)H oxidase-derived ROS in HBMECs.

3) Long Zhao, Li-Na Sun, Hui-Bin Nie, Xue-Ling Wang, Guang-Ju Guan. Berberine Improves Kidney Function in Diabetic Mice via AMPK Activation. **PLOS ONE**, 2014; 9(11):e113398 (DOI: 10.1371/journal.pone.0113398)



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PLOS ONE

Berberine Improves Kidney Function in Diabetic Mice via AMPK Activation

Long Zhao, Li-Na Sun, Hui-Bin Nie, Xue-Ling Wang, Guang-Ju Guan*

Nephrology Research Institute, the Second Hospital of Shandong University, Jinan, Shandong, China

Abstract

Diabetic nephropathy is a major cause of morbidity and mortality in diabetic patients. Effective therapies to prevent the development of this disease are required. Berberine (BBR) has several preventive effects on diabetes and its complications. However, the molecular mechanism of BBR on kidney function in diabetes is not well defined. Here, we reported that activation of AMP-activated protein kinase (AMPK) is required for BBR-induced improvement of kidney function in vivo. AMPK phosphorylation and activity, productions of reactive oxygen species (ROS), kidney function including serum blood urea nitrogen (BUN), creatinine clearance (Ccr), and urinary protein excretion, morphology of glomerulus were determined in vitro or in vivo. Exposure of cultured human glomerulus mesangial cells (HGMCs) to BBR time- or dose-dependently activates AMPK by increasing the thr172 phosphorylation and its activities. Inhibition of LKB1 by siRNA or mutant abolished BBR-induced AMPK activation. Incubation of cells with high glucose (HG, 30 mM) markedly induced the oxidative stress of HGMCs, which were abolished by 5-aminoimidazole-4-carboxamide ribonucleoside, AMPK gene overexpression or BBR. Importantly, the effects induced by BBR were bypassed by AMPK siRNA transfection in HG-treated HGMCs. In animal studies, streptozotocin-induced hyperglycemia dramatically promoted glomerulosclerosis and impaired kidney function by increasing serum BUN, urinary protein excretion, and decreasing Ccr, as well as increased oxidative stress. Administration of BBR remarkably improved kidney function in wildtype mice but not in AMPKα2-deficient mice. We conclude that AMPK activation is required for BBR to improve kidney function in diabetic mice.

Citation: Zhao L, Sun L-N, Nie H-B, Wang X-L, Guan G-J (2014) Berberine Improves Kidney Function in Diabetic Mice via AMPK Activation. PLoS ONE 9(11): e113398. doi:10.1371/journal.pone.0113398

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

Funding: This work was supported by the National Key Technology Research and Development Program of the Ministry of Science and Technology of China 2011BAI10B05.

Competing Interests: The authors have declared that no competing interests exist.

* Email: guangj@sdu.edu.cn

The similarities in the three articles (KJPP, Brain Inj., Exp Mol Pathol) are striking, and the person who advised us of this situation says the full papers are almost identical.

We have written to the corresponding authors (Min Hu & Bo Liu) of the paper published in our journal and have asked for a prompt response.

We have received response from the corresponding author (Bo Liu) as follow:

Dear Hunjoo Ha,

We asked an agency to write and submit this paper to KJPP. Even we do not know this paper contains substantial overlap with other papers. We are sorry for such serious scientific misconduct.

As a result, we want to withdraw this paper.

We are very sorry to bring you and KJPP the inconvenience.

Liu

In addition, we inform you another serious issue about the above KJPP paper. During the revision process of the KJPP paper, the title and authors in the revised manuscript are completely changed from those of the original manuscript (correspondence: Zhan Liu) submitted to KJPP. We regret this carelessness during the review process. The followings summarize the titles and lists of authors from the original version and revised version of the KJPP manuscripts.

1) Original version:

Title: Activation of AMPK attenuates lipopolysaccharide-impaired the integrity and function of blood-brain barrier in microvascular endothelial cells

Authors: Zhihong Zhao[1,*], Jue Hu[2,*], Xiaoping Gao[1], Hui Liang[1], and Zhan Liu[3]
[1]Department of Neurology, The First Affiliated Hospital (People's Hospital of Hunan Province), Hunan Normal University, Changsha, Hunan, China; [2]Department of Neurology, Changsha Central Hospital, Changsha, Hunan, China; [3]Department of Gastroenterology, The First Affiliated Hospital (People's Hospital of Hunan Province), Hunan Normal University, Changsha, Hunan, China.

Correspondence: Zhan Liu or Zhihong Zhao, People's Hospital of Hunan Province, No. 61 West Liberation Road, Changsha City, Hunan 410005, China. Tel: 86-731-82278048; Fax: 86-731-82278012; Email: liuzhan2004@126.com. (* Two authors contribute equally to this work)

2) Revised version:

Title: Resveratrol attenuates lipopolysaccharide-induced dysfunction of blood-brain barrier in endothelial cells via AMPK activation

Authors: Min Hu[1,*], MD and PhD, Bo Liu[2,*], MD
[1]Department of Biomedical Engineering, College of Engineering, Peking University, Beijing, China; [2]Deapartment of orthopaedics, the Third Xiangya Hospital, Central South University, Changsha, China.

Correspondence: *Correspondence to Min Hu or Bo Liu, No.5, Yiheyuan Road, Haidian District, Peking University, Beijing, China, 100871. Email: hu15084737958@139.com or Liu1367251@163.com

Recently, we have received another submission from Zhan Liu, and it was found that the manuscript was totally fabricated with pictures from papers published in J Biol Chem (2009; 284(25): 17120–17128), Brain Inj (2015; 29(6): 777–784), and Exp Mol Pathol (2014; 97: 386–392). The title of this manuscript is “Hyperglycemia via activation of thromboxane A2 receptor impairs the integrity and function of blood-brain barrier in microvascular endothelial cells”. If you need evidences for this affair, we can provide them.

In addition, Western Blots (GAPDH) pictures shown in Brain Injury (Fig-6b), Exp Mol Pathol (Fig-5B), and Korean J Physiol Pharmacol (Fig-6B) were identical to the WB (AMPK) picture (Fig-2A) published in **PLOS ONE** (2014; 9(11):e113398, DOI: 10.1371/journal.pone.0113398).

As you may notice, we strongly suspect that **Zhan Liu** (Department of Gastroenterology, The First Affiliated Hospital (People's Hospital of Hunan Province), Hunan Normal University, Changsha, Hunan, China) has to explain all of these matters. We suspect also that, Zhan Liu had been submitted the same manuscript to at least three Journals (Exp Mol Pathol, Brain Inj, Korean J Physiol Pharmacol) from October 2013 to January 2014.

1) **Exp Mol Pathol:** Received 24 February 2014; and in revised form 27 August 2014; Accepted 10 September 2014; Available online 16 September 2014

2) **PLOS ONE:** Received June 9, 2014; Accepted October 23, 2014; Published November 19, 2014

3) **Brain Injury:** Received 28 October 2013; Revised 15 November 2014; Accepted 4 January 2015; Published online 20 March 2015

4) **Korean J Physiol Pharmacol:** Received November 7, 2013; Revised July 8, 2015; Accepted January 3, 2016; Published July 1, 2016

If all of our journals agree that this is a case of duplicate publication, we will need to determine which version of the paper should remain public and noted as the “version of record” and which paper should be retracted, in accordance with policies and procedures governing academic publication. Please note the publication dates and history provided above.

We (KJPP) have decided to retract the article published in KJPP (Korean J Physiol Pharmacol 2016 Jul; 20(4): 325-332) with a “Retraction by Editors” in next issue of our Journal (01 March, 2017).

We hope you will agree with this course of action. Please let us know if you have any questions.

Sincerely,

Hunjoo Ha & Tong Mook Kang

Editors-in-Chief

Korean Journal of Physiology and Pharmacology

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